Diagnostic accuracy of conventional cervical cytology (papanicolau smear), liquid based cytology (LBC) and visual inspection with acetic acid (VIA) in detecting premalignant and malignant cervical lesions among Filipino women in a tertiary hospital*

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ABSTRACT

Objective: Cervical cancer screening can reduce both the incidence and mortality rates of the disease. This study aimed to assess the diagnostic accuracy of conventional cytology, liquid based cytology and visual inspection with acetic acid in detecting pre-malignant and malignant cervical lesions.

Methods: There were 249 patients who participated in the study. Of these, 6/249 (2.4%) turned out positive in papsmear, 7/249 (2.8%) turned out positive in liquid based cytology while 23/249 (9.2%) turned out positive in visual inspection with acetic acid. Colposcopic guided cervical biopsy was done on all 249 patients to confirm the results.

Results: Fourteen turned out positive for cervical intraepthelial neoplasia, 1 patient had carcinoma in situ and 1 was positive for squamous cell carcinoma.

Conclusion: Among the three screening tests, VIA appears to be the most accurate, followed by liquid based cytology as compared to the conventional papsmear.

Keywords: *Cervical Cancer Screening, Papsmear, Liquid Based Cytology, Visual Inspection with Acetic Acid, Colposcopic Guided Biopsy*

INTRODUCTION

Cervical cancer remains to be the second most common malignancy and is the most common cause of cancer-related mortality among Filipino women since the early 1990s. Every year, the government and several medical societies worked tirelessly trying to eardicate this deadly disease. Several information campaigns were made, screening programs were started, yet the incidence remained the same, with an annual age-standardized incidence rate of 22.5 cases per 100,000 women, with a 5 year survival rate of 44% and mortality rate of 1 per 100,000.[1] Based on the Philippine HPV and related cancers 2017 fact sheet, Philippines has 34.30 million women 15 years old and beyond who are at risk to develop cervical cancer. Current estimates indicate that every year 6,670 women are diagnosed with cervical cancer and 2,832 die from the disease. Despite being a preventable disease, it has a high mortality rate and a low survival rate. These have been attributed to the late diagnosis, often already in advanced stage. In countries like Australia and Rwanda, precursor lesions were detected early and treated. These countries may be one of the first to eradicate cervical cancer. In the Philippines, however, implementation of a nationwide screening has been less successful.

Cervical cytology is the most widely used screening method. It is based on detecting abnormal or premalignant cells being shed by the cervical epithelium. Cervical cytology has been in use for more than 50 years, and has proven itself as one of the mainstays in screening for cervical cancer.[2,3] Currently, two types of cervical cytology tests are in use - the conventional type, also known as

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the Papanicolau smear, and the more recent liquid based cytology.

Conventional cervical cytology like the Papanicolau smear has been in use since the 1960s and is credited with successfully reducing the incidence and mortality of cervical cancer in many developed countries.[4,5] However, meta-analyses of the accuracy of conventional papsmear test have reported widely varying false negative rates and investigations into the sources of false negative errors have concluded that the majority are due to sampling errors, that is, no abnormal cells are found on the smeared slide upon review.[3,6] Based on several meta-analyses, both the sensitivity and specificity of this tool is relatively low (30-87% sensitivity, 86% to 100% specificity).[7-9] The liquid based cytology on the otherhand was introduced in the mid-1990s to address these issues. Its advantages include an increase in the detection of high grade cervical intraepithelial neoplasia, a reduction in the number of unsatisfactory and "satisfactory-but-not-limited-by" specimens, and provision of residual cellular material for subsequent molecular testing.[10]

The visual inspection with acetic acid was first described by Ottaviano and La Torre in 1981. It gained popularity as an alternative to cytology in screening for cervical cancer in poorly resourced locations because of its availability and affordability. This uses 3-5% acetic acid applied on the cervix, and after application, visual inspection without the aid of any instrument is done. This naked-eye examination is based on the principle that upon application of the acetic acid, the epithelial tissues, columnar and abnormal squamous epithelial areas swell, causing reversible coagulation or precipitation of cellular proteins. If the epithelium contains a lot of cellular proteins like those seen in premalignant cells, acetic acid coagulates these proteins resulting in acetowhitening, which is seen distinctly as compared with the normal pinkish color of the surrounding normal squamous epithelium of the cervix.[11]

In 2001, Ngelangel et. al. compared the validity and acceptability of acetic acid visualization (VIA), magnified acetic-acid visualization (VIAM) and papsmear taken using spatula and cotton swab and papsmear taken using cervical brush, in the detection of premalignant and malignant lesions of the cervix.[12] In their study, the acetic acid visualization and magnified acetic acid visualization have been recommended for initial cervical cancer screening in the Philippines as compared to papsmear. Based on this study, the accuracy of papsmear results suggest a low specificity and sensitivity that is consistent with local and international studies.

In order to effectively protect the population from cervical cancer, two key elements must be in place: The maximum number of adult women must be reached with the screening test, and the quality and effectiveness of the test itself must be unquestionable.[3] The screening test that is to be used must be as accurate as possible.

It is based on this premise that this study was conceptualized. We aimed to determine which screening tool is best for each situation. In this study, Filipino women ages 21-65 years old were chosen as subjects. Unlike most studies done on cervical cancer screening, this is a prospective cross-sectional study wherein all the participants were subjected to all the three screening methods, and all results were confirmed by a colposcopic guided biopsy.

OBJECTIVE

General Objective

To determine the diagnostic accuracy of conventional cervical cytology, liquid based cytology and visual inspection with acetic acid in detecting pre-malignant and malignant cervical lesions among Filipino women ages 21 to 65 years old in a tertiary hospital.

Specific Objectives

1. To compare the diagnostic accuracy of papsmear, liquid based cytology and visual inspection with acetic acid in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

2. To determine the age groups that are predominantly at risk for premaligant and malignant cervical lesions.

3. To determine if there is a significant difference between the risk factors such as parity, age of first coitus, number of sexual partners and smoking, and the incidence of premalignant and malignant cervical lesions.

MATERIALS AND METHODS

Subjects

This is prospective cross-sectional study conducted at a tertiary government hospital outpatient clinic from August 2017 to July 2018. At least 243 asymptomatic Filipino women, ages 21-65 years old who came in for papsmear were invited to paticipate in the study. Each patient had papsmear, liquid based cytology, visual inspection with acetic acid and colposcopic guided biopsy on the same day. Patients who were pregnant, previously diagnosed with a premalignant cervical lesion or cervical carcinoma, had a prior treatment for cervical intraepithelial neoplasia and those who had previous hysterectomy were excluded from the study. The order of the procedure were as follows: the liquid based cytology and conventional papsmear were collected alternately.

After the specimen collection, visual inspection with acetic acid was done and was followed by the colposcopic guided biopsy. A 4th year OB-GYN resident performed the collection of papsmear and liquid based cytology while the VIA and the colposcopic guided biopsy was done by the principal investigator. The papsmear, liquid based cytology and the cervical tissue biopsies were read by a senior pathology resident, confirmed by 2 consultants who are fellows of the Philippine Society of Pathologists/ Cytologists. The researchers were blinded of the results. The pathologist and the OB-GYN resident were not aware of the VIA and colposcopy findings while the OB-GYN resident and principal investigator were not aware of the papsmear, LBC and cervical biopsy results. All findings were collated at the end of the study.

Ethical Considerations and Consent

This study was conducted in accordance with the ethical principles based on the Declaration of Helsinki and the National Guidelines for Biomedical Research of the National Ethics Committee (NEC) of the Philippines. The research protocol was evaluated and approved by the Ethics Committee and the Institutional Review Board (IRB) of the hospital. All patients who participated in the study had informed and written consent. Participation in the study was purely voluntary and without financial compensation. The results and patient information was kept strictly confidential by the investigators. A unique alphanumeric code was issued to each patient and their names did not appear on any of the data collection tools.

Smear Collection Technique

Papanicolau Smear

For each subject, a sample of cervical cells were taken using a cervical broom. A standard glass slide was prepared for each subject and cervical cells taken smeared on the slide and fixed using 95% ethyl alcohol. Another sample of cervical cells were taken using the same collection device and was placed in the liquid based preparation.

The conventional cytology smears were obtained using the cervical broom. The cervical broom has a flat array of plastic strips contoured to conform to the cervix, with longer strips in the middle allowing simultaneous sampling of the endocervix and ectocervix. The middle strips which are longer, were inserted into the cervical os until the shorter outer strips bend upon touching the ectocervix. After insertion of the broom into the endocervical canal, some bristles should still be visible to avoid inserting the broom too far. Inserting the broom too far can cause inadvertent sampling of the lower uterine segment, resulting to diagnostic difficulties because its epithelium resembles a high-grade squamous intraepithelial lesion and adenocarcinoma in situ. Once inserted into the cervical os, the broom was rotated three times. To transfer the material collected from the cervix, the sides of the broom was stroked once across the slide followed by immediate fixation. Immediate fixation is important and a critical step to prevent air-drying artifact, which can distort the cells and affects the interpretation. The smears were immersed directly into a container filled with 95% ethyl alcohol.[9]

Liquid Based Cytology

The liquid based cytology was performed using the SurePath Pap Test. SurePath Pap Test was developed by TriPath Imaging for the collection of samples in an ethanol-based transport medium. The tip of the cervical broom were included in the sample vial. Hettich centrifuge and a PrepStain robotic sample processor with computer and monitor were used to prepare the slides. Other materials collected that could obscure the results were eliminated by dense centrifugation. LBC prepares an evenly distributed deposit of cells in a circle 13 mm in diameter. It also included a final staining step that discretely stains each individual slide.[13]

VIA Procedure

The patient was placed in a lithotomy position on the examining table. After proper positioning, observation of the external genitalia and perineal region was done. Any signs of excoriations, edema, vesicles, papules, sores, ulceration and warts were reported. A sterile vaginal speculum was inserted to view the cervix. The external os and the squamocolumnar junction were identified. The secretions and mucus were gently wiped off using a cotton ball with normal saline solution. 5% acetic acid was applied on the cervix using a soaked cotton ball for 1 minute. After removing the cotton ball, the cervix was examined for any acetowhite changes particularly in the transformation zone close to the squamocolumnar junction. The results one minute after application of acetic acid were recorded on the VIA form.[14]

Colposcopy Guided Biopsy

After the VIA, the patient rested for 30 minutes while the procedure for colposcopy was being explained. The patient was also advised to take Mefenamic Acid 500 mg tabletor Paracetamol 500 mg tablet 30 minutes before the procedure. The participant was placed in a lithotomy position on an examining table with stirrups. The vaginal speculum was inserted followed by inspection of the cervix. Lubricant was applied on the speculum prior to being inserted into the cervix. On speculum examination, the nature of the secretions of the cervix and vagina were noted, likewise any other obvious findings such as polyp,

ectropion, nabothian cysts, inflammation, atrophy and infection, leukoplakia (hyperkeratosis), ulcer, condylomata and any obvious lesion. Mucus was removed gently from the cervix with cotton balls drenched in saline solution. Rough manipulation was avoided because it can cause loss of epithelium and bleeding. The green filter of the colposcope was used in the examination of the blood vessels, enhancing the contrast, and by using higher levels of magnification, noting the borders of the transformation zone. 5% acetic acid was applied to the cervix with cotton balls, covering the entire cervical surface. This procedure helped in the coagulation and removal of mucus, allowing the acetic acid to penetrate on the epithelium fully. The cervix was observed for any acetowhitening effect of acetic acid. This was followed by the application of Lugol's iodine solution. The cervix was also observed for iodine uptake. Biopsy was done on suspicious areas. For those with normal colposcopic findings, biopsy was done randomly within the transformation zone. Hemostasis was done by applying Monsel's solution to the biopsied area. The findings were documented and explained to the participants. All subjects underwent colposcopy and cervical punch biopsy on the same day that thepapsmear and liquid based cytology specimens were obtained, and VIA was done. This was to ensure patients' adherence to the study as well as to eliminate the possibility of being lost to follow-up should they be asked to return for colposcopy and biopsy.

Reporting of Results

The conventional papsmear and liquid based cytology results were reported using the Bethesda nomenclature. All the results of the visual inspection with acetic acid and the colposcopic guided biopsy were being recorded in a standard form used by the institution.

Statistical Analysis

Frequency and percentage were used to describe the variables of the study such as age, parity, age of first coitus, number of sexual partners, and smoking (pack years). These were also used evaluate the premalignant and malignant cervical lesions using papsmear, LBC, and VIA. Diagnostic test such as sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC) were used to compare the diagnostic reliability of papsmear, liquid based cytology and visual inspection with acetic acid.

Chi-square test was used to determine the significant difference between age, parity, age of firstcoitus, number of sexual partners, and smoking (pack years) and the incidence of pre-malignant and malignant cervical lesions.

SPSS version 25 was used for data analysis. Microsoft excel was used for data encoding. Null hypotheses were rejected at α 0.05 level of significance.

LIMITATION OF THE STUDY

Human Papilloma Virus (HPV) DNA testing was not done due to the limited funding for this study. However, we recommend to include HPV DNA analysis on subsequent studies.

RESULTS

A total of 249 patients were included in the study. Majority of the patients were 36 to 50 years old with more than 50% of the overall samples. The average parity among the female patients were 2 to 3 with 39% and 4 to 5 with 27.3%. 80.3% of the patients had their sexual debut at age 16 to 25 years old. 37.3% were with only one sexual partner while 32.1% had 2 to 3 partners and 14.1% had 4 to 5 sexual partners. There were only 35 patients or 14.1% who were smokers, of which 77.1% of them were smoking for less than 5 pack years.

On papsmear, there were 6 cases or 2.4% who had positive result. LBC turned out positive in 7 cases or 2.8% while VIA reported 23 cases or 9.2% who had positive result. The gold standard, colposcopic guided biopsy, reported 16 cases or 6.4% with premalignant or malignant cervical lesion.

Table 3 presents the sensitivity, specificity, NPV, PPV, AUC, accuracy and significance of the papsmear, LBC, and VIA on colposcopic guided biopsy.

Sensitivity is the probability of detecting premalignant and malignant cervical lesions using papsmear, LBC, and VIA when colposcopic guided biopsy is positive (True Positive). Specificity is the probability of not detecting premalignant and malignant cervical lesions using Papsmear, LBC, and VIA when colposcopic guided biopsy is negative (True Negative). Positive predictive value is the probability of the presence of premalignant and malignant cervical lesions using papsmear, LBC and VIA when colposcopic guided biopsy detects it. Negative predictive value is the probability of the absence of premalignant and malignant cervical lesions using papsmear, LBC, and VIA when premalignant and malignant cervical lesions is absent. AUC or area under the curve is the coefficient or magnitude of how well the papsmear, LBC and VIA detects a positive outcome.

Papsmear has a sensitivity of 18.6% (4.1 – 45.7%), specificity of 98.7% (96.3 – 99.7%), PPV of 50% (11.8 – 88.2%) and NPV of 94.7% (91.0 – 97.1%). The AUC of the screening test was 0.59 and it was significant, in favor of higher accuracyin detecting a negative outcome correctly than a positive outcome.

Table 1. Patient profile.

		Frequency	Percent
Age	21-25	6	2.4%
	26-30	19	7.6%
	31-35	29	11.6%
	36-40	45	18.1%
	41-45	40	16.1%
	46-50	43	17.3%
	51-55	37	14.9%
	56-60	17	6.8%
	>61	12	4.8%
Parity	Nullipara	16	6.4%
	Primipara	39	15.7%
	2-3	97	39.0%
	4-5	68	27.3%
	6-7	20	8.0%
	>7	2	0.8%
Age of 1st Coitus	Null (Zero)	1	0.4%
	<15	12	4.8%
	16-20	121	48.6%
	21-25	79	31.7%
	26-30	22	8.8%
	31-35	5	2.0%
	>35	2	0.8%
Number of Sexual Partners	Only One	93	37.3%
	2-3	80	32.1%
	4-5	35	14.1%
	6-7	19	7.6%
	7-8	1	0.4%
	9-10	4	1.6%
	>10	10	4.0%
Smoking (Pack Years)	Non-smoker	207	83.1%
	Smoker	35	14.1%
	<5	27	77.1%
	6-10	3	8.6%
	11-15	2	5.7%
	>20	3	8.6%
Total		**249**	**100.0%**

Table 2. Screening tests and biopsy results.

		Frequency	Percent
Papsmear	Positive	6	2.4%
	Negative	243	97.6%
LBC	Positive	7	2.8%
	Negative	242	97.2%
VIA	Positive	23	9.2%
	Negative	226	90.8%
Colposcopic Guided Biopsy	Positive	16	6.4%
	Negative	233	93.6%
Total		**249**	**100.0%**

LBC has a sensitivity of 43.8% (19.8 – 70.1%), specificity of 100% (98.4 – 100%), PPV of 100% (11.8 – 88.2%) and NPV of 96.3% (93.1 – 98.3%). The AUC of this screening test was 0.72 and it was significant in favor of a higher reliability in detecting positive outcome correctly (both positive and negative). In comparison with papsmear, LBC was found to be more accurate than papsmear.

VIA has a sensitivity of 87.5% (61.7 – 98.5%), specificity of 96.1% (92.8 – 98.2%), PPV of 60.9% (38.5 – 80.3%) and NPV of 99.1% (96.8 – 99.9%). The AUC of the diagnostic test was 0.92 and it was significant, in favor of higher accuracy in detecting premalignant and malignant cervical lesions correctly (both positive and negative). In comparison with papsmear and LBC, 14 cases were correctly identified as confirmed by colposcopic guided biopsy. This is higher than 7 cases correctly identified using LBC and 3 cases from papsmear. With the highest AUC, VIA was more accurate than papsmear and LBC.

Age was not a significant risk factor for premalignant and malignant cervical lesions. Parity was significant with p-value of below 0.05, revealing that patients with 6-7 deliveries are at risk for having a premalignant and malignant cervical lesion. Age of first coitus, number of sexual partners, smoking and number of pack years were not significant with p-value above 0.05.

Colposcopic guided biopsy was done on all 249 patients. The findings were recorded and reported.

DISSCUSSION

Despite being a preventable disease, cervical cancer is one of the leading cause of morbidity and mortality among women worldwide. Eighty five percent of cervical cancer patients live in developing countries. Many screening programs were introduced and implemented in the Philippines since the early 1980's, yet have failed to reduce the mortality rates. The WHO in 2002 estimated that only 5% of women are screened appropriately in developing countries. Possible reasons for failure in screening programs include insufficient access and lack of funding in rural areas where most of the population in developing countries reside. There was also lack of awareness and education as to need for screening. Poor patient follow-up was also noted. Approximately 50% of all cancers occur in developing countries like the Philippines, yet only a fraction of the resources are allotted for the fight against cancer worldwide. In a study by Domingo et. al. in 2009, they concluded that cervical cancer has remained a leading cancer in women in the Philippines but organized programs have yet to be implemented, largely due to high costs and needs for infrastructure within the health system.[15] After almost a decade, cervical cancer still

able 3. Diagnostic test of premalignant and malignant cervical lesions using papsmear, LBC, and VIA

		Colposcopic Guided Biopsy		Sensitivity	Specificity	PPV	NPV	AUC	P-value
		P	N						
Papsmear	P	3	3	18.6%	98.7%	50%	94.7%	0.59	0.000
	N	13	230	4.1 – 45.7%	96.3 – 99.7%	11.8 – 88.2%	91.0 – 97.1%		
LBC	P	7	0	43.8%	100%	100%	96.3%	0.72	0.000
	N	9	233	19.8 – 70.1%	98.4 – 100%	59 – 100%	93.1 – 98.3%		
VIA	P	14	9	87.5%	96.1%	60.9%	99.1%	0.92	0.000
	N	2	224	61.7 – 98.5%	92.8 – 98.2%	38.5 – 80.3%	96.8 – 99.9%		

P – Positive; N – Negative

Table 4. Age, parity, age of first coitus and smoking as risk factors for premalignant and malignant cervical lesions.

		Colposcopic Guided Biopsy				P-value
		Positive		Negative		
		F	%	F	%	
Age	21-25	0	0.0%	6	2.6%	0.85
	26-30	2	13.3%	17	7.5%	0.72
	31-35	2	13.3%	27	11.9%	0.82
	36-40	3	20.0%	42	18.5%	0.85
	41-45	4	26.7%	36	15.9%	0.44
	46-50	3	20.0%	40	17.6%	0.92
	51-55	0	0.0%	37	16.3%	0.16
	56-60	1	6.7%	16	7.0%	0.64
	>61	1	6.7%	11	4.8%	0.80
Parity	Nullipara	1	6.7%	15	6.6%	0.61
	Primipara	1	6.7%	38	16.7%	0.48
	2-3	7	46.7%	90	39.6%	0.77
	4-5	0	0.0%	68	30.0%	0.02
	6-7	6	40.0%	14	6.2%	0.00
	>7	0	0.0%	2	0.9%	0.30
Age of 1st Coitus	.00	0	0.0%	1	0.4%	0.06
	<15	2	13.3%	10	4.4%	0.32
	16-20	7	46.7%	114	50.2%	0.99
	21-25	5	33.3%	74	32.6%	0.83
	26-30	1	6.7%	21	9.3%	0.92
	31-35	0	0.0%	5	2.2%	0.76
	>35	0	0.0%	2	0.9%	0.30
Number of Sexual Partners	Only One	4	26.7%	89	39.2%	0.47
	2-3	7	46.7%	73	32.2%	0.36
	4-5	0	0.0%	35	15.4%	0.18
	6-7	2	13.3%	17	7.5%	0.72
	7-8	0	0.0%	1	0.4%	0.06
	9-10	1	6.7%	3	1.3%	0.53
	>10	1	6.7%	9	4.0%	0.90
Smoking (Pack Years)	Non-smoker	14	93.3%	193	85.0%	0.59
	Smoker	1	6.7%	34	15.0%	0.59
	<5	1	100.0%	26	76.5%	0.60
	6-10	0	0.0%	3	8.8%	0.13
	11-15	0	0.0%	2	5.9%	0.05
	>20	0	0.0%	3	8.8%	0.13

remains a leading cause of cancer among Filipino women.

Papanicolaou smear has been used for decades since its discovery by Dr. Papanicolaou in 1943 as a screening tool to detect premalignant lesions of the cervix that would later lead to cervical malignancy.[16] The appropriateness of a screening test depends not only on its accuracy as measured mainly by sensitivity and specificity but also on its simplicity and safety.

There are conflicting evidences regarding the conventional papsmear versus liquid based cytology. In a randomized control study by Siebers, the liquid-based cytology does not perform better than conventional papsmear in terms of relative sensitivity and PPV for detection of cervical cancer precursors.[17] But the problem with most of these studies is they lack adequate reference standards. Only 1 analysis met the standard criteria. In a population-based study of 8636 women, liquid based cytology was significantly more sensitive than the conventional smears at detecting high-grade squamous intraepithelial lesions (HSIL) and cancer, with sensitivity rates of 92.9% and 100% vs 77.8% and 90.9%, respectively (P<.001). This evidence demonstrates that the liquid based cytology is better at detecting cervical cancer.[18]

In a study by Lee et. al in 1997, the liquid based cytology has been shown to significantly increase the detection of low grade and high grade intraepithelial lesions, as it significantly improved specimen adequacy.[19] Likewise, Simon et. al also reported that LBC can detect some entities such as atypical squamous cell of undetermined significance (ASCUS), atypical glandular cells not otherwise specified (AGCNOS), and high grade squamous intraepithelial lesion (HSIL) associated to adenocarcinoma in situ (AIS).[20] Singh et. al, noted in his study that LBC technique leads to significant reduction of unsatisfactory sample rate. LBC samples had better clarity, uniform spread of smears, shorter screening time and can handle hemorrhagic and inflammatory samples better. In terms of sensitivity and specificity, LBC had equivalent sensitivity and specificity as compared to conventional papsmear based on this study.[21]

In a study by Ronco et. al. they randomized more than 45,000 women (age range, 25–60) to undergo cervical cancer screening with either conventional or liquid-based cytology. The endpoint was long-term rates of histologically confirmed cervical intraepithelial neoplasia (CIN) grade 2 or higher. Compared with conventional cytology, liquid-based cytology had a higher sensitivity for detecting CIN grade 1, but not CIN grade 2 or higher, when both atypical cells of undetermined significance and low-grade intraepithelial lesions were used as cut-off points for colposcopy. In fact, liquid-based cytology had a significantly lower positive predictive value for all CIN endpoints. However, liquid-based cytology did significantly reduce the number of results considered unsatisfactory because of obscuring inflammation.[22]

In our study, liquid based cytology performed better than conventional papsmear showing better sensitivity, specificity, PPV and NPV. This showed that LBC had better yield, eliminating red blood cells and inflammatory cells.

One of the more popular alternative methods for cervical cancer screening is visual inspection with acetic acid. This method has gained popularity especially in developing countries. It has proven itself in many researches that it is an adequate alternative to papsmear. Pre-cancerous lesions contain higher intracellular proteins, turning white when combined with acetic acid. A normal cervix without any precancerous lesions remains the same after acetic acid application. VIA is a good or even better alternative to papsmears because it is easier to use, more affordable and requires fewer physician visits. Currently, to perform a pasmear, the physician needs a speculum, lamp, slide, cytobrush and a microscope. The results are released by the pathologist after 2 weeks or more on follow-up visit. With VIA, any trained physician can use a speculum can do the test with cotton swab drenched in 3-5 % acetic acid. There is no pathologist needed. If the test is negative, the patient can be informed of the result immediately without right after the procedure. In rural areas where people travel for several hours for a doctors' visit, a screening method like VIA will have a much higher success rate because it requires fewer visits to the doctor. In this study, the accuracy of VIA was evaluated in comparison to papsmear and liquid based cytology, using colposcopic guided biopsy as the gold standard. Many studies have been published comparing VIA and papsmears, or comparing papsmears with liquid based cytology as a screening method for cervical cancer. Most studies compared VIA with papsmears, looking at sensitivities and specificities of both, while comparing them to colposcopy with biopsy as the gold standard. Gaffikin published a small meta-analysis in 2003. In his publication, test qualities of papsmears vary, ranging from 11% to 99%. The study also concluded that VIA was comparable to papsmears in terms of detecting high grade lesions or cancer. It was also mentioned that although a lower specificity of VIA was noted in various publications, it was unanimously concluded that VIA was useful as an adjuvant or alternate to cytology.[19]

In the Philippines, Ngelangel conducted four different screening exams as follows - visual inspection with acetic acid, magnified visualization with acetic acid (VIAM), spatula + cotton swab papsmear and cervical brush papsmear. Sensitivities for these four tests were found to be at 37% for VIA, 34.1% for VIAM, 14.3% for spatula papsmear and 19.1% for cervical brush papsmear. The specificity rates were at 90.7%, 90.7%, 97.5%, and 97.9%,

Table 5. Colposcopic findings of patients with a positive finding on either one or more screening tests.

			Frequency
Papsmear	**Biopsy**	**Colposcopic Findings**	
LSIL	Cervicitis	Ectropion, Cryp Opening	1
LSIL	CIN I	Dense Acetowhitening, Fine Mosaic	1
ASCUS	Cervicitis	Ectropion	2
HSIL	CIN II	Dense Acetowhitening, Sharp Borders, Coarse Mosaic and Punctations	1
HSIL	CIS	Dense Acetowhitening, Coarse Mosaic and Punctations	1
LBC	**Biopsy**	**Colposcopic Findings**	
LSIL	CIN I	Dense Acetowhitening, Fine Mosaic, Irregular Border	1
LSIL	CIN I	Dense Acetowhitening, Fine Mosaic	1
LSIL	CIN I	Thin Acetowhitening	1
LSIL	SCCA	Dense Acetowhitening, Persistent Acetowhitening, Coarse Mosaic, Sharp Borders	1
ASCUS	CIN I	Thin Acetowhitening	1
HSIL	CIN II	Dense Acetowhitening, Sharp Borders, Coarse Mosaic and Punctations	1
HSIL	CIS	Dense Acetowhitening, Coarse Mosaic and Punctations	1
VIA	**Biopsy**	**Colposcopic Findings**	
Positive	CIN I	Thin Acetowhitening	2
Positive	CIN I	Thin Acetowhitening, Fine Mosaic and Punctations	1
Positive	CIN I	Thin Acetowhitening, Sharp Borders	1
Positive	CIN I	Dense Acetowhitening, Course Mosaic, Sharp Borders	1
Positive	CIN I	Dense Acetowhitening, Fine Mosaic, Irregular Border	1
Positive	CIN I	Dense Acetowhitening, Fine Punctations	1
Positive	CIN I	Dense Acetowhitening, Fine Mosaic	2
Positive	CIN II	Dense Acetowhitening, Sharp Borders, Coarse Mosaic and Punctations	1
Positive	CIN II	Dense Acetowhitening, Course Mosaic, Sharp Borders	1
Positive	CIN III	Dense Acetowhitening, Coarse Punctuations	1
Positive	CIS	Dense Acetowhitening, Coarse Mosaic and Punctations	1
Positive	Cervicitis	Dense Acetowhitening	2
Positive	Cervicitis	Dense Acetowhitening, Sharp Borders	2
Positive	Cervicitis	Dense Acetowhitening, Ectropion	2
Positive	Cervicitis	Dense Acetowhitening, Ectropion, Nabothian Cysts, Cryp Opening	1
Positive	Cervicitis	Thin Acetowhitening	1
Positive	Cervicitis	Ectropion, Dense Acetowhitening	1
Positive	SCCA	Dense Acetowhitening, Persistent Acetowhitening, Coarse Mosaic, Sharp Borders	1

**Gray highlights were positive findings matched with biopsy.*

respectively. VIA had the highest sensitivity among the four tests and was recommended for initial cervical cancer screening in the Philippines.[12]

Another study by Toral, et. al done in 2004 also concluded that VIA was more sensitive than papsmear and recommended that adding VIA to papsmear adds the PPV and the specificity of the test. Therefore, VIA is a useful adjunct to papsmear.[23]

DOH evaluated VIA as a screening method in Cameroon, Africa, where majority of cancer deaths in women are due to malignancies of the breast and cervix. All patients had VIA and papsmear. If any of these two tests were positive, patients were subjected to colposcopy with biopsy. For control, one out of ten ''negative'' cervices were biopsied. Acetowhite lesions with at least a border close to the squamo-columnar

Table 6. Summary of the Colposcopic Findings of Patients

	Frequency	Percentage
Cervicitis N=12		
Dense Acetowhitening	8	66.7%
Ectropion	7	58.3%
Cryp Opening	2	16.7%
Sharp Borders	2	16.7%
Nabothian Cysts	1	8.3%
Thin Acetowhitening	1	8.3%
CIN I N=10		
Dense Acetowhitening	5	50.0%
Fine Mosaic and Punctations	5	50.0%
Thin Acetowhitening	4	40.0%
Sharp Borders	2	20.0%
Course Mosaic	1	10.0%
Ectropian	1	10.0%
Irregular Boarder	1	10.0%
CIN II N=3		
Coarse Mosaic and Punctations	3	-
Dense Acetowhitening	2	-
Sharp Borders	2	-
No Acetowhitening	1	-
No Lesions	1	-
CIN III N=1		
Coarse Punctations	1	-
Dense Acetowhitening	1	-
CIS N=1		
Coarse Mosaic and Punctations	1	-
Dense Acetowhitening	1	-
SCCA N=1		
Coarse Mosaic	1	-
Dense Acetowhitening	1	-
Persistent Acetowhitening	1	-
Sharp Borders	1	-

junction were considered as significant and positive. Those with faint borders were reported as low grade and those with sharp borders were reported high grade. Those with no white epithelium were reported negative. Outcomes of this study showed that the sensitivity of VIA was 70.4% vs 47.7% for papsmear, while VIA specificity was at 77.6% vs 94.2% for papsmear. PPV of VIA was reported at 44% and NPV at 91.3%. Doh concluded that, although papsmear has slightly better testing qualities, VIA has acceptable test qualities and may, in low resource settings be implemented as a large scale screening method.[10]

In 2005, after many evidence based articles proving VIA as an adequate screening method for cervical cancer, Lawrence went to Guatemala and started a pilot study, evaluating VIA with the ''see and treat'' method. 1052 women were invited to participate in the study. Lawrence evaluated on the acceptability of VIA as a screening tool for cervical cancer followed by immediate cryotherapy for CIN findings among women in rural Guatemala. Among the 954 women screened, 13% were positive, consistent with CIN I or higher. Almost all women with positive findings on VIA agreed to be treated immediately with cryotherapy. This result showed that the ''see-and-treat'' method with VIA could benefit women in developing countries. The drawback of this study was that cytology or histology was not done to confirm the results of VIA. The women were treated immediately assuming that the VIA test was accurate. However, they reported that the result of this study was comparable to other similar studies in the region.[10]

In assessing the risk factors, only parity of 6-7 was

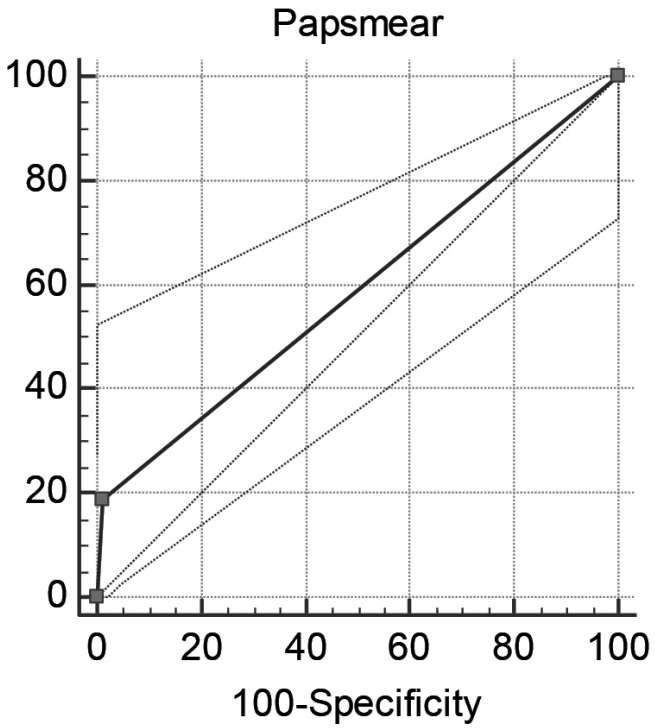

Figure 1. ROC curve of papsmear and biopsy

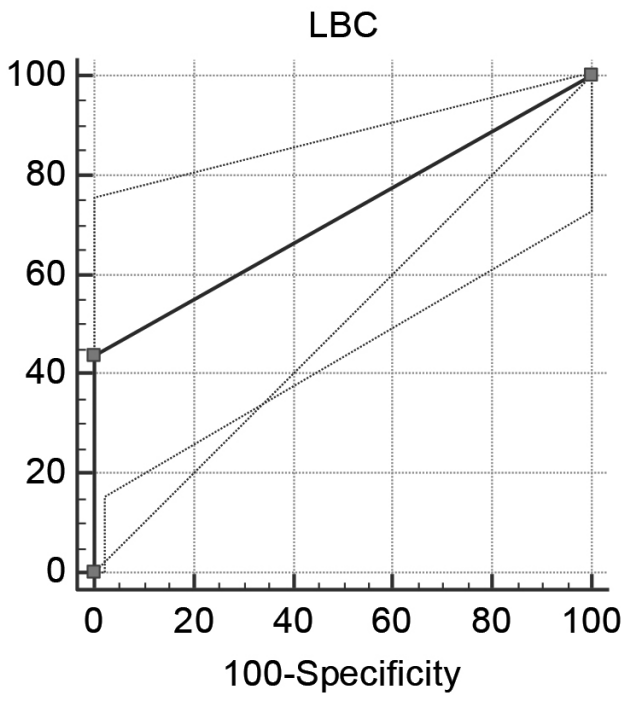

Figure 2. ROC curve of LBC and biopsy

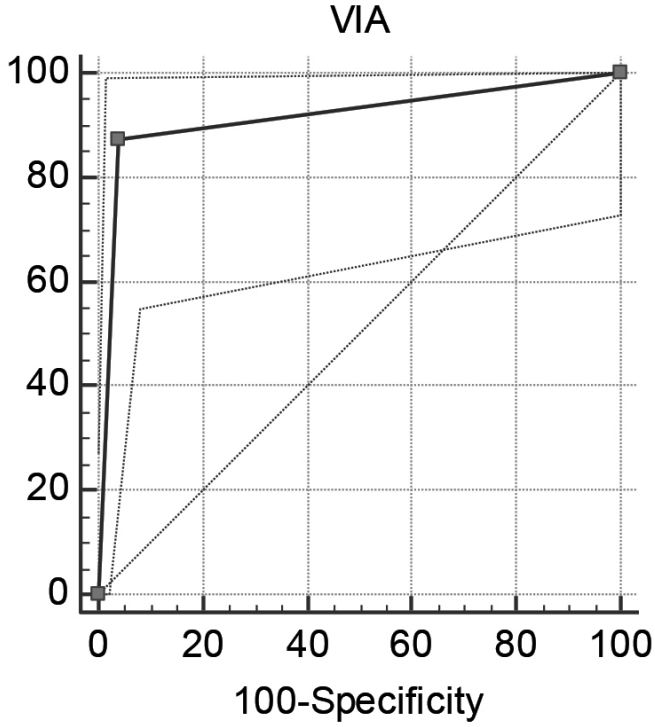

Figure 3. ROC curve of VIA and biopsy

noted to be significant. Based on the American Cancer Society, women with 3 or more full pregnancies are at risk of developing cervical cancer. Initiation of sexual contact younger than 17 years old almost doubles the risk of cervical cancer.[1] In our study however, we only have 2 patients who had their first coitus at less than 15 years old and 1 patient at 16 years old. Our study showed age of first coitus is not a risk factor. Number of sexual partners and smoking are also not significant risk factors in our study.

On colposcopy, it was noted in our study that the findings of atypical vessels were only noted among patients with premalignant and malignant lesions. Based on the study of Sillman, et. al., presence of atypical vessels on colposcopy increases the chance of having a premalignant lesion.[24]

CONCLUSION

This study has shown that VIA is an adequate and acceptable screening method for cervical cancer. In low-resource areas, VIA is better than papsmear and LBC because it is easy to perform and is more affordable. VIA has a very high NPV, which means that when a test is negative, the women can go home reassured that she is not likely to have a premalignant or malignant cervical lesion; eliminating the need for follow-up visits. The low PPV of VIA however, present the problem of many false positives,

which may discourage the see-and-treat method. On the other hand, PPV is dependent on the incidence, and if a see-and-treat method was implemented in a high-risk population with a high incidence of cervical cancer, the qualities of the VIA test may improve. For a more accurate yield, we can also combine VIA and a cervical cytology test in screening patients for premalignant cervical lesions.

For patients with inflammation or cervicitis, LBC is a better alternative than conventional papsmear and VIA since VIA has high false positive rates for patients with active infection.

The VIA, colposcopy and biopsy in this study was performed by a gynaecologic oncology fellow in training while the collection of specimen for cytology, both liquid based and papsmear was done by an OB-GYN senior resident. Although standardization and proper collection techniques were followed, this variable should also be taken into consideration since these screening tools are also operator dependent.

RECOMMENDATIONS

HPV DNA test may be included in future studies.This study was also done among asymptomatic women only. An analysis comparing the results of this study can be done among symptomatic groups. This might increase the yield of positive results and might give us a better correlation with the risk factors. ■

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